REMARKS

Applicant response to the Examiners action of 22 September 2005. In that action the Examiner rejected claims 82-91 and 94-95 under 35 U.S.C. § 112. In addition, claims 82,83,86-88, 103 and 106 were rejected under § 102 and § 103 of the patent laws based on the Moncada et al. or Kobzik et al. or Fujisawa et al. references. In addition the Ikeda reference was cited as being anticipatory of claims 82, 86-88, 103, and 105 of the present application. Claims 82-106 are again presented. Claims 82 and 83 have been currently amended to eliminate the term "particular". Claims 90 and 91 have been amended to change their dependency from claim 82 to claim 83 to avoid duplication of claims 87 and 88 and claim 106 has been cancelled.

The term "polymer mimicking and artificial antibody" and "phage display binding site" are intended to leave the conventional meanings in art of biochemistry. Applicant will provide this information to the Examiner by separate cover if needed. Also, claims 82 and 83 are independent of one another. Therefore, the term "polymer" cannot be considered an antibody, rather it would be classified under the "binding entity" of claim 83.

It is believed the sequence listing ID 29 covers the page 32, region 25-42, covering A3 plus A4.

A terminal disclaimer is enclosed to overcome the non-statutory double patenting rejection and a PTO 2038 form for the

requisite fee is attached.

The Moncada reference does not teach the production of an antibody, either polyclonal or monoclonal to human iNOS. Moncada only indicates that there is a need for these antibodies. Moncada's experiments reveal only one immunoassay which is in the form of a Western blot using a polyclonal anti-mouse antiserum that cross-reacts with human iNOS. As is stated in Moncada, antibodies to proteins are very useful. However, such expression of need is different from the revelation of a teaching of an invention to meet such need. Simply stated, Moncada does not teach applicants invention by the showing of monoclonal antibody, binding entity, or vehicle which specifically recognizes human iNOS, without cross-reacting with human nNOS or human eNOS.

Kobzik shows the employment of two different rabbit polyclonal antibodies for immunolocalization experiments. One polyclonal antibody consisted of an anti-rat brain cNOS type (whole protein immunogen). The other polyclonal antibody consisted of an anti-mouse iNOS (1-20) anti-peptide antibody. Kobzic pages 374, 376, and 377, suggest that a different iNOS is present and is being missed with the employment of the anti-mouse iNOS (1-20) anti-peptide antiserum. Thus, the only teaching of Kobzic is a poor anti-peptide polyclonal antiserum that weakly cross-reacts with human iNOS. In any case, Kobzik does not anticipate or render applicants invention obvious.

Fujisawa describes a polyclonal rabbit anti-rat iNOS antibody

for Western blot only. The Oshima reference found in Fujisawa depicted an induction of iNOS via an injection of P. acnes and LPS. Oshima used partially purified rat liver iNOS that had been completely denatured by boiling in SDS-PAGE sample buffer. The Western blot of control rat liver showed at least 6 distinct other bands in addition to the iNOS band. Immunoprecipitation of the sample produced only a single NOS band on Western blots. The antiserum did not react strongly with mouse macrophage iNOS. The wide band in the induced lanes, Fig. 3a, lanes 3, 5, and 7, indicate both rat iNOS and rat eNOS are being recognized. No cross-reaction data with eNOS was presented. Since mouse and rat iNOS antiserum cross-reacted very weakly with mouse macrophage iNOS, it would seem highly unlikely that the Fujisawa antiserum would recognize human iNOS, since human iNOS is more distantly related. There is also no mention of a monoclonal antibody to iNOS in Fujisawa. It is highly likely that cross-reaction with eNOS occurs in Fujisawa since the antiserum disclosed therein was not characterized eNOS. Moreover the denaturing by boiling of the Fujisawa sample in SDS-PAGE sample buffer would have destroyed any conformational epitopes that might have existed. Thus, there is no teaching in Fujisawa as to monoclonal antibodies or any entities specifically recognizing human iNOS enzymes without cross-reacting with human eNOS or human nNOS enzymes.

Ikeda describes a carboxyl terminal "side" 14 amino acids in length as a peptide conjugated to KLH. This peptide / KLH

conjugate was used as an immunogen to raise rabbit polyclonal antisera. Very little characterization of the antiserum is disclosed. In fact, no monoclonal antibodies were used or discussed in the Ikeda reference. The Sherman reference referred to by Ikeda provides DNA and amino acid sequences for hiNOS in a human tumor cell line, and shows that a polyclonal anti-mouse iNOS antiserum cross-reacts with their preparations of hiNOS. Ikeda describes histochemical staining and Western blots using a polyclonal anti-peptide antibody. This histochemical staining is inconsistent with human iNOS localization, and indicates that the antiserum is also staining eNOS. See Fig. 9 and legend. It is also stated on page 17 of the Ikeda reference, lines 18 through 26 that such cross-reaction with eNOS occurred in Western blots. Again, no monoclonal antibodies were used or discussed in the Ikeda reference. It is believed that the anti-peptide antibody described in Ikeda cannot be used for clinical diagnostics for human iNOS since there is cross-reaction with human eNOS.

Thus, it is believed that the claims as submitted are novel and unobvious from the prior art cited taken alone or in combination. The passing to issue of the application at an early date is earnestly solicited.

Respectfully submitted,

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